EXHIBIT 18

A POPULATION-BASED STUDY OF SEIZURES AFTER TRAUMATIC BRAIN INJURIES

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ABSTRACT

Background The risk of seizures is increased after traumatic brain injury, but the extent and duration of the increase in risk are unknown. The purpose of this study was to identify the characteristics of brain injuries that are associated with the development of seizures.

Methods We identified 4541 children and adults with traumatic brain injury (characterized by loss of consciousness, post-traumatic amnesia, or skull fracture) in Olmsted County, Minnesota, during the period from 1935 through 1984. Injuries were classified as mild (loss of consciousness or amnesia lasting less than 30 minutes), moderate (loss of consciousness for 30 minutes to 24 hours or a skull fracture), or severe (loss of consciousness or amnesia for more than 24 hours, subdural hematoma, or brain contusion). We compared the incidence of new unprovoked seizures in this cohort with population rates, using standardized incidence ratios and Cox proportional-hazards analysis.

Results The overall standardized incidence ratio was 3.1 (95 percent confidence interval, 2.5 to 3.8). The standardized incidence ratio was 1.5 (95 percent confidence interval, 1.0 to 2.2) after mild injuries but with no increase over the expected number after five years, 2.9 (95 percent confidence interval, 1.9 to 4.1) after moderate injuries, and 17.0 (95 percent confidence interval, 12.3 to 23.6) after severe injuries. In the multivariate analysis, significant risk factors for later seizures were brain contusion with subdural hematoma, skull fracture, loss of consciousness or amnesia for more than one day, and an age of 65 years or older.

Conclusions The increased risk of seizures after traumatic brain injury varies greatly according to the severity of the injury and the time since the injury. (N Engl J Med 1998;338:20-4.)

THERE have been many studies of seizures after penetrating war injuries.[1-3] However, most studies of post-traumatic seizures in civilian populations involve selected neurosurgical series.[4,5] The overall risk of seizures is as high as 53 percent after war injuries[2] and ranges from 1.8 to 5.0 percent in civilian populations.[5,6] Much less is known about the characteristics of traumatic brain injury in civilians that are associated with an increased risk of seizures and the magnitude and duration of the increase.

We studied post-traumatic seizures in Olmsted County, Minnesota, for the 50-year period from 1935 through 1984, with follow-up extended to the end of 1994. This study is a continuation of our study of post-traumatic seizures during the interval from 1935 through 1974,[6] but it includes additional cases during the period from 1975 through 1984, as well as additional follow-up of the original cohort.

METHODS

Cases of traumatic brain injury were identified through the Medical Records Linkage System of the Rochester Epidemiology Project at the Mayo Clinic. This system includes diagnoses made for inpatient, outpatient, and emergency room visits, even if they did not result in hospitalization.[7] Diagnoses that potentially represented traumatic brain injuries were reviewed (head injury, skull fracture, subdural hematoma, brain contusion, accidental injury, concussion, and loss of consciousness). Since these diagnoses included all lacerations and contusions to the face and skull as well as more serious injuries, only about 10 percent of the diagnoses met our criteria for head injury with evidence of brain involvement. Between 1935 and 1984, a total of 5984 injuries met our criteria for traumatic brain injury.

Not all the patients who had traumatic brain injuries were included in the evaluation of post-traumatic seizures. Of the total of 5984 episodes of traumatic brain injury, 98 were in patients known to have epilepsy, and these patients were considered ineligible for a study of the post-traumatic onset of seizures. The 626 patients who had fatal traumatic brain injuries (defined as injuries resulting in death within one month) were also excluded from further evaluation. In addition, we excluded 397 patients who had had second or subsequent episodes of traumatic brain injury and 322 patients with head injuries that were not ascertained directly but were discovered as a result of the sequelae of the injuries, such as headaches or visual problems. Thus, 4541 patients were included in our evaluation of post-traumatic seizures.

The patients were followed from the date of recovery from the traumatic brain injury to the occurrence of a subsequent unprovoked seizure (97 patients), a subsequent traumatic brain injury (334), death (373), intracranial surgery (10), migration from the eight-county area of southeastern Minnesota (1139), or the last follow-up in 1995 (2588). For inpatients, the date of recovery was defined as the date of hospital discharge, except when other injuries prolonged the hospital stay, in which case the date of termination of care by the neurologic service was recorded as the recovery date. For outpatients and patients seen in the emergency room but not admitted, the recovery date was defined as the day after the patient was seen. Follow-up was truncated in the case of migration from southeastern Minnesota because of the difficulty of ascertaining and classifying late seizures in patients who had moved.

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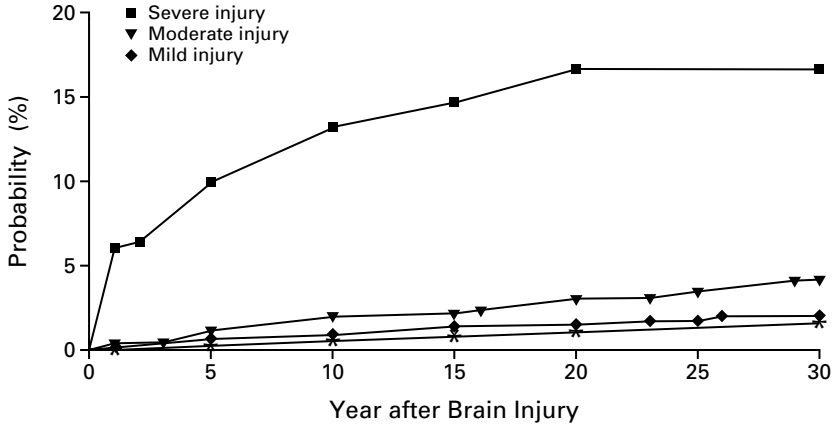

No. of Patients				
Mild injury	2758	1751	1191	609
Moderate injury	1455	934	660	351
Severe injury	328	181	136	74
Total	4541	2866	1987	1034

Figure 1. Cumulative Probability of Unprovoked Seizures in 4541 Patients with Traumatic Brain Injuries, According to the Severity of the Injury and the Incidence of Seizures in the General Population.

The cumulative incidence in the population was derived from incidence rates,[8] with the use of the density method to convert the rates to risk estimates.[9] The asterisks indicate the incidence in the general population at specified points in time.

Clinical and demographic information was collected on the circumstances and characteristics of the traumatic brain injuries. The clinical features that were documented included the presence and duration of loss of consciousness or antegrade or retrograde amnesia, the presence and type of skull fracture, the presence of cerebral contusion or subdural or epidural hematomas, and the presence of early seizures. Early seizures were defined as those occurring in the first week after the injury; however, in injuries with a protracted course (e.g., infection or recurrent subdural hematoma), the period of early seizures was extended to a month. Only 16 of the 117 patients who had early seizures had the first seizure more than one week after the injury.

Seizures occurring after recovery from traumatic brain injury (late seizures) were ascertained from medical records. The records of possible seizures were reviewed for potential inclusion by one of us. Of the 143 patients with seizures after recovery from traumatic brain injury, 97 were classified as having unprovoked seizures; 46 patients were classified as having acute symptomatic seizures associated with an acute structural or metabolic central nervous system insult (in 41) or fever (in 5). We did not evaluate the effect of anticonvulsant drugs on late seizures, because only 35 of the 4541 patients received these drugs for six months or longer.

Statistical Analysis

The analysis included only post-traumatic unprovoked seizures as an outcome. The observed numbers of unprovoked seizures were compared with the expected numbers, which were based on the age- and sex-specific incidence rates in Rochester, Minnesota, for the initial diagnosis of an unprovoked seizure disorder and on person-years of follow-up.[8] The cumulative probability of an unprovoked seizure after traumatic brain injury was estimated with the use of the Kaplan–Meier method. The cumulative incidence in the population was based on the density method of converting rates to risk.[9] The importance of prognostic factors was determined by Cox proportional-hazards analysis.[10]

As in our prior study,[6] we divided the traumatic brain injuries into three categories of clinical severity. Severe traumatic brain injuries were characterized by one or more of the following features: brain contusion (diagnosed on the basis of observation during surgery or focal neurologic symptoms), intracranial hematoma, or loss of consciousness or post-traumatic amnesia for more than 24 hours. Moderate traumatic brain injuries were characterized by one or more of the following features: loss of consciousness or post-traumatic amnesia lasting 30 minutes to 24 hours or a skull fracture. Mild traumatic brain injuries were characterized by an absence of fracture and a loss of consciousness or post-traumatic amnesia for less than 30 minutes.[6] For this analysis, we further divided the mild traumatic brain injuries into those with a documented loss of consciousness and those with only amnesia. Brain contusion was diagnosed by computed tomography (CT) only during the last 10 years of our 50-year study, and none of the 34 patients with mild or moderate traumatic brain injuries and abnormalities on CT had seizures.

RESULTS

The age distribution of the patients with traumatic brain injuries was as follows: birth to 4 years, 542 patients; 5 to 14 years, 1184 patients; 15 to 64 years, 2546 patients; and 65 years or older, 269 patients. The cohort was followed for a total of 53,222 person-years, with the follow-up period ranging from days to decades. During follow-up, 97 patients had unprovoked seizures, of whom 22 had only one seizure and 75 had multiple seizures.

Figure 1 shows the cumulative probability of seizures in the cohort according to the severity of the traumatic brain injury and the incidence of seizures in the general population. The five-year cumulative

TABLE 1. STANDARDIZED INCIDENCE RATIOS FOR SEIZURES AMONG 4541 PATIENTS WITH TRAUMATIC BRAIN INJURY, ACCORDING TO THE SEVERITY OF THE INJURY.

SEVERITY OF INJURY*	NO. OF CASES		STANDARDIZED INCIDENCE RATIO (95% CI)†
	OBSERVED	EXPECTED	
Mild	28	18.4	1.5 (1.0–2.2)
Moderate	30	10.5	2.9 (1.9–4.1)
Severe	39	2.3	17.0 (12.3–23.6)
Total	97	31.2	3.1 (2.5–3.8)

*Patients with mild injuries had a loss of consciousness or post-traumatic amnesia for less than 30 minutes, with no skull fracture; those with moderate injuries had a loss of consciousness or post-traumatic amnesia for 30 minutes to 24 hours or a skull fracture; and those with severe injuries had a brain contusion or intracranial hematoma or a loss of consciousness or post-traumatic amnesia for more than 24 hours.

†CI denotes confidence interval.

TABLE 2. STANDARDIZED INCIDENCE RATIOS FOR SEIZURES ACCORDING TO THE SEVERITY OF TRAUMATIC BRAIN INJURY AND THE INTERVAL AFTER THE INJURY.

INTERVAL AFTER INJURY (YR)	NO. OF PATIENTS*	NO. OF CASES		STANDARDIZED INCIDENCE RATIO (95% CI)†
		OBSERVED	EXPECTED	
Mild injury				
<1	2758	5	1.6	3.1 (1.0–7.2)
1–4	2483	11	5.2	2.1 (1.1–3.8)
5–9	1751	4	4.3	0.9 (0.3–2.6)
≥10	1191	8	7.4	1.1 (0.5–2.1)
Moderate injury				
<1	1455	6	0.9	6.7 (2.4–14.1)
1–4	1307	9	2.9	3.1 (1.4–6.0)
5–9	934	7	2.3	3.0 (1.2–6.2)
≥10	660	8	4.4	1.8 (0.8–3.6)
Severe injury				
<1	328	19	0.2	95.0 (58.4–151.2)
1–4	275	10	0.6	16.7 (8.4–32.0)
5–9	181	6	0.5	12.0 (4.5–26.6)
≥10	136	4	1.0	4.0 (1.1–10.2)

*The number of patients is the number being followed at the beginning of the interval.

†CI denotes confidence interval.

probability was 0.7 percent in patients with mild injuries, 1.2 percent in those with moderate injuries, and 10.0 percent in those with severe injuries. The 30-year cumulative incidence was 2.1 percent for mild injuries, 4.2 percent for moderate injuries, and 16.7 percent for severe injuries.

The expected number of seizures in the 4541 patients, on the basis of the age-specific incidence rates in Rochester, Minnesota, was 31.2. The standardized incidence ratio was 3.1 (95 percent confidence interval, 2.5 to 3.8). However, the overall standardized incidence ratio is misleading because of the large differences in risk according to the severity of the injury and the duration of follow-up.

Table 1 shows the standardized incidence ratios according to the severity of the injury. The incidence of seizures was clearly increased in the group of patients with severe or moderate traumatic brain injuries but only marginally increased in the group with mild injuries.

For all patients with mild traumatic brain injuries, the standardized incidence ratio was 3.1 in the first year after the injury and 2.1 for the next four years (Table 2), but there was little or no increase over the expected number of seizures thereafter. The standardized incidence ratio for the first five years after the injury was slightly higher among the patients with mild traumatic brain injuries and loss of consciousness (2.5; 95 percent confidence interval, 1.2 to 4.4) than among those with mild injuries and only post-traumatic amnesia (2.1; 95 percent confidence interval, 0.7 to 4.9). The elevated risk of unprovoked seizures among the patients with mild traumatic brain injuries was not explained by the presence of early seizures, since none of the 36 patients with mild injuries and early seizures also had late unprovoked seizures.

Among the patients with severe traumatic brain injuries, the risk of seizures was elevated during the first year of follow-up (standardized incidence ratio, 95.0) and remained significantly elevated throughout follow-up (Table 2). Among the patients with moderate traumatic brain injuries, the risk of seizures was markedly increased for up to 10 years after the injury, but not thereafter (Table 2).

In addition to the 97 patients with unprovoked seizures, there were 46 patients with acute symptomatic seizures. The symptomatic seizures were related to ethanol withdrawal (in 20 patients), cerebrovascular disease (in 7), fever (in 5), toxic insults (in 4), other metabolic insults (in 4), tumors (in 4), and multiple acute insults (in 2).

The high incidence of seizures related to ethanol withdrawal (20 cases, as compared with 4.6 expected cases) was not related to the severity of the brain injury. In the group of patients with mild injuries, there were 10 cases of withdrawal-related seizures, as compared with 2.8 expected cases (standardized in-

TABLE 3. RATE RATIOS FOR SEIZURES AFTER TRAUMATIC BRAIN INJURY.*

VARIABLE	TRAUMATIC BRAIN INJURIES	LATE SEIZURES	RATE RATIO (95% CI)†		
			UNIVARIATE	MODEL 1	MODEL 2
	no. of patients				
Brain contusion or subdural hematoma	37	13	30.3 (16.6–55.2)	11.3 (4.7–27.3)	12.1 (5.2–28.0)
Brain contusion only	159	19	8.9 (5.3–14.8)	5.0 (2.5–10.0)	5.0 (2.6–9.8)
Subdural hematoma only	36	4	9.8 (3.6–27.1)	6.3 (2.2–18.0)	6.7 (2.3–19.1)
Linear fracture and age ≥5 yr or depressed fracture	527	35	4.1 (2.7–6.2)	—	2.0 (1.2–3.2)
Linear fracture and age ≥5 yr	313	17	3.3 (1.9–5.6)	2.2 (1.3–3.8)	—
Depressed fracture	214	18	5.2 (3.1–8.9)	1.8 (0.94–3.3)	—
Loss of consciousness or post-traumatic amnesia for more than 24 hr	176	24	8.4 (5.3–13.3)	1.9 (0.97–3.6)	1.9 (0.98–3.6)
Early seizure	117	12	5.5 (3.0–10.1)	1.4 (0.7–2.7)	—
Age ≥65 yr	269	10	2.5 (1.3–4.9)	2.2 (1.1–4.4)	2.2 (1.1–4.4)

*The data are based on a Cox proportional-hazards analysis.

†In model 1, linear skull fracture in a patient five years old or older and depressed skull fracture are separate variables, and early seizure is included as a variable. In model 2, linear and depressed skull fractures are combined as a single variable, and early seizure is excluded. CI denotes confidence interval.

cidence ratio, 3.6; 95 percent confidence interval, 1.7 to 6.6). The increase in the incidence of seizures related to ethanol withdrawal was presumably a result of the relation between ethanol ingestion and traumatic brain injury, even among the patients with mild traumatic brain injuries.

Table 3 shows the rate ratios for late seizures according to clinical and demographic factors. The strongest univariate association was between the presence of a brain contusion or subdural hematoma and late seizures. Because brain contusion and subdural hematoma had both independent effects and a joint effect (through an interaction) on the subsequent risk of seizures, three variables were used in the multivariate models: concurrent brain contusion and subdural hematoma, brain contusion alone, and subdural hematoma alone. In both multivariate models, brain contusion alone and subdural hematoma alone remained the strongest risk factors. The factors in model 1 were brain contusion, subdural hematoma, loss of consciousness or post-traumatic amnesia lasting more than 24 hours, linear skull fracture in a patient 5 years old or older, depressed skull fracture, an age of 65 years or older, and early seizure. In model 2, linear skull fracture and depressed skull fracture were combined into a single factor, and early seizure was excluded.

Among children under the age of five years with linear fractures, there was a slightly increased rate of seizures (rate ratio, 1.5; 95 percent confidence interval, 0.5 to 4.8). The univariate rate ratio was 3.3 for linear fractures in patients five years old or older and 5.2 for depressed fractures in patients of any age (Table 3). The rate ratio for depressed fractures was lower in the multivariate analysis than in the univariate analysis because depressed fractures were often accompanied by intracranial lesions. Because of the similar rate ratios, depressed and linear fractures in persons five years old or older were combined in model 2.

The presence of early seizures (in 117 of the patients) was also a strong risk factor for late seizures in the univariate analysis (rate ratio, 5.5), but the rate ratio for early seizures was only 1.4 when the analysis was adjusted for the other factors. Since the strong prognostic effect of early seizures was almost entirely eliminated by adjustment for other prognostic factors, this variable was excluded from model 2.

Loss of consciousness or amnesia was categorized according to duration: less than 30 minutes, 30 minutes to 24 hours, or more than 24 hours. The rate ratio was 8.4 for a duration of more than 24 hours as compared with one of less than 30 minutes. For the 570 patients who had loss of consciousness or post-traumatic amnesia lasting from 30 minutes to 24 hours, the relative risk of post-traumatic seizures was 1.0. Thus, only loss of consciousness or post-traumatic amnesia for more than 24 hours remained a prognostic factor.

The rate ratio for unprovoked seizures in persons 65 years old or older, as compared with those younger than 65, was 2.5, which is approximately the same as the ratio of incidence rates for those two age groups in the general population.[8]

DISCUSSION

We found a strong relation between the severity of traumatic brain injury and the risk of subsequent unprovoked seizures. We also found that the severity of the injury was correlated with the interval during which the risk of seizures was increased. The risk of late seizures after severe traumatic brain injury fell rapidly but persisted throughout the follow-up period in our study. Thus, even unprovoked seizures occurring more than 10 years after a severe traumatic brain injury can be attributed in large part to the injury.

The estimated relative risk of seizures after penetrating war injuries is very high: 580 during the first year and 25 during the first 10 years, as compared with the risk in the general population.[2] In our earlier study,[6] we found a moderate but not significant excess of seizures after mild traumatic brain injuries. In this study, with a much larger cohort, we found an excess risk of 1.5 (95 percent confidence interval, 1.0 to 2.2) among persons with mild traumatic brain injuries, and the risk in this group continued to be elevated for five years.

The increased incidence of unprovoked seizures after mild traumatic brain injury may be an artifact if the ascertainment of subsequent unprovoked seizures was more accurate in our cohort of patients with traumatic brain injuries than in the entire population of Rochester, Minnesota, which was used for comparison. For the Rochester incidence study,[8] cases were identified through the Rochester Epidemiology Project, whereas for this study, all medical records were reviewed, and any entries suggesting a seizure were reviewed and classified by one of us. However, we compared the ascertainment of cases with the two methods and found that over 90 percent of unprovoked seizures ascertained in the follow-up study were identified in the incidence study.[6] In addition, the standardized incidence ratios for the low-risk groups in this study and in other cohort studies are close to 1.0 and therefore not spuriously increased.[11,12]

The increased incidence of subsequent unprovoked seizures in the group with mild traumatic brain injuries may have been due to characteristics of the patients and not to the injuries themselves. The patients with mild injuries may for some reason have been at higher risk for unprovoked seizures. On the other hand, the absence of an increased risk of unprovoked seizures in this large group more than five years after the injury does not support either a constitutional predisposition or differential ascertainment as an explanation of the overall increase.

In our evaluation of post-traumatic seizures in a large cohort of civilians who sustained traumatic brain injury, brain contusion and subdural hematoma were the strongest risk factors for late seizures, and the increased risk of seizures in patients with these factors persisted for at least 20 years. Skull fractures and prolonged loss of consciousness were significant but weaker predictors of late seizures. For patients with mild, closed head injuries and loss of consciousness or post-traumatic amnesia for less than 30 minutes, there was a moderate, twofold increase in risk only until the fifth year after the injury.

Supported by grants (NS16308 and AR30582) from the National Institutes of Health.

We are indebted to Ms. Pat Perkins, R.N., who collected data for this study.

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